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April 30, 1999

Anticipating resistance plasmids

Dr. Gail Cassell
Lilly Research Labs
Indianapolis, IN 46285

Dear Gail -

I present this to you very succinctly: you know the background very well. So, in a nutshell:

Natural history has long been mined for new antibiotics. Now the band wagon is parasite genomics, to focus targetting of antimicrobials, and associated with this, mutational studies to try to anticipate the development of resistance.

However, the most likely source of resistance to new antibiotics will be plasmids and cassettes probably already extant in the microbial world. Missing is a concerted project to mine the biosphere for such plasmids, and that is what I propose. It is probably too much to expect to develop a systematic taxonomy and resource collection of all relevant plasmids, though that would be an ultimate desideratum.

A small part of the overall effort would be devoted to selection with commonplace germicides and environmental stresses (including UV, heat, soap, dissection) for correlation with antibiotic resistance. This may help illuminate current debates about the possible unsalutary implications of pushing germicides into the environment.

Many modes of antibiotic resistance are organized into cassettes, and it will be important to see how xenobiotic-resistance is coupled with other repertoires.

We would certainly focus on antibiotic drug prospects you have in the pipeline. The aim would be to be able to anticipate plasmid-borne resistance before it becomes manifest as treatment failure in the clinic. I am proposing that we set this up as a collaborative project in my lab at R.U. I would recruit a postdoc and a technician for a 3-year program: estimated budget (fully burdened) would be \$200,000 per year. I do have other prospects for support for this line of research, but I thought to give you first crack at it -- I know you will let me know in timely fashion whether this is a reasonable thing for Lilly to support.

Fishing expeditions don't fare well at NIH, but if we start getting positive results with exotic antibacterials we might try to shift the fiscal support for this program to NIH grant applications. My colleague David Thaler would be an important part of our team. Please let me know asap, one way or the other, if you're able to entertain this proposal.

Plasmids can be phenotyped only by transferring them into a host; but an array of methods is available, most generally DNA transfection.

Basic protocol.

So DNA from (miscellaneous cultures isolated from) biosphere sources would be transfected into

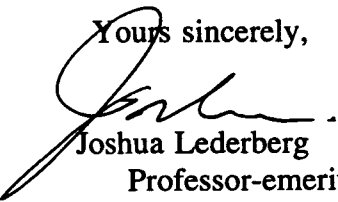
- a) E. coli = ideal for genetic analysis
- b) B. subtilis = second best
- c) other critical target species

and the transfected populations are then put through the selective filters of antibiotic challenge. Plasmid conferring resistance would then be isolated, cloned etc. for further characterization. This would then be the basis for assessment as to the likelihood of clinically significant importation of this genre of plasmids into the target species.

There is some role for primary selection on the natural inocula. However this will be encumbered by many microflora bearing non-specific modes of resistance.

I'll bring a copy of this with me, in hopes of seeing you at NPAP in Washington next week.

Yours sincerely,



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Professor-emeritus

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